ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Tidal Breathing Measurements at Discharge and Clinical Outcomes in Extremely Low Gestational Age Neonates

Clement L. Ren[1], MD, MBA, Rui Feng[2], PhD, Stephanie D. Davis[1], MD, Eric Eichenwald[3], MD, Alan Jobe[4], MD, PhD, Paul E. Moore[5], MD, Howard B. Panitch[3], MD, Jack K. Sharp[6], MD, Jeff Kisling[1], RRT, Charles Clem[1], RRT, and James S. Kemp[7], MD for the Prematurity and Respiratory Outcomes Program*

*A complete list of investigators, research staff, and participating sites of the Prematurity and Respiratory Outcomes Program is listed in the Appendix available in the online supplement.

[1]Riley Children's Hospital, Indianapolis, IA; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [3]Children's Hospital of Philadelphia, Philadelphia, PA; [4]Children's Hospital Medical Center, Cincinnati, OH; [5]Vanderbilt University School of Medicine, Nashville, TN; [6]Texas Children's Hospital, Houston, TX; [7]Washington University, St. Louis, MO

Corresponding Author:
Clement L. Ren, MD, MBA
Division of Pediatric Pulmonology, Allergy, and Sleep Medicine
Riley Hospital for Children
705 Riley Hospital Drive
Indianapolis, IN 46202
Phone: 317-948-9994
FAX: 317-944-7247
Email: clren@iu.edu

Author Contributions: CLR, RF, and JSK led the project. CLR, SDD, EE, AJ, PEM, HBP, JKS, and JSK contributed to the design of the study and to data collection. CC and JK performed RIP data analysis. CLR, RF, JSK, SDD, EE, AJ, PEM, HBP, and JKS analyzed and interpreted the data. CLR, RF, and JSK wrote the first draft of the manuscript. All the authors reviewed and approved the final version of the manuscript.

Sources of Support: NIH grants U01 HL101794, U01 HL101456, U01 HL101798, U01 HL101813, U01 HL101465, U01 HL 101800, and 5RO1 HL105702.

Word Count: 3,991

Running Title: Tidal Breathing and Clinical Outcomes in Preterm Infants

Keywords: Wheezing, respiratory inductance plethysmography, pulmonary function tests, oximetry, premature

---

Abstract

Rationale: The relationship between respiratory function at hospital discharge and the severity of later respiratory disease in extremely low gestational age neonates is not well defined.

Objectives: To test the hypothesis that tidal breathing measurements near the time of hospital discharge differ between extremely premature infants with BPD or respiratory disease in the first year of life compared to those without these conditions.

Methods: Study subjects were part of the Prematurity and Respiratory Outcomes Program (PROP) study, a longitudinal cohort study of infants born <29 gestational weeks followed from birth to 1 year of age. Respiratory inductance plethysmography was used for tidal breathing measurements before and after inhaled albuterol 1 week prior to anticipated hospital discharge. Infants were breathing spontaneously and were receiving ≤1 liter per minute (lpm) nasal cannula flow at 21-100% FiO_2. A survey of respiratory morbidity was administered to caregivers at 3, 6, 9, and 12 months corrected age to assess for respiratory disease. We compared tidal breathing measurements in infants with and without bronchopulmonary dysplasia (BPD, oxygen requirement at 36 wk) and with and without respiratory disease in the first year of life. Measurements were also performed in a comparison cohort of term infants.

Results: 765 infants survived to 36 weeks post-menstrual age, with research-quality tidal breathing data in 452 out of 564 tested (80.1%). Among these 452 infants, the rate of post-discharge respiratory disease was 65.7%. Compared to a group of 18 term infants, PROP infants had abnormal tidal breathing patterns. However, there were no significant differences in tidal breathing measurements in PROP infants who had BPD or who had respiratory disease in the first year of life compared to those without these diagnoses. Bronchodilator response was not

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

significantly associated with respiratory disease in the first year of life.

Conclusions: Extremely premature infants receiving <1 lpm nasal cannula support at 21-100% FiO_2 have tidal breathing measurements that differ from term infants, but these measurements do not differentiate those preterm infants who have BPD or will have respiratory disease in the first year of life from those who do not.

Clinical trial registered with ClinicalTrials.gov (NCT01435187)

Abstract Word Count: 344

Premature birth is associated with impaired lung function that can persist into adulthood [1]. Wheezing, cough, and hospitalization for respiratory illnesses all occur more frequently in children born preterm than in those born at term [2]. Although bronchopulmonary dysplasia (BPD) is a risk factor for more severe respiratory problems, infants without BPD also experience substantial respiratory morbidity [3]. Despite the high prevalence of respiratory problems in preterm children, there is a paucity of data regarding the physiologic mechanisms of post-prematurity respiratory disease.

Pre-morbid respiratory function among infants born at term is an independent predictor of wheezing and asthma in infancy and early childhood [4-8]. Infant pulmonary function tests (PFTs) performed in preterm infants between 36-40 weeks postmenstrual age (PMA) have shown decreased expiratory flows, reduced functional residual capacity (FRC), increased airway resistance, and decreased lung compliance [9-12]. However, most studies using infant PFTs in preterm infants had small sample sizes and limited follow-up data collected several months after discharge, making it difficult to establish an association between lung function near the time of discharge from the neonatal intensive care unit (NICU) and subsequent respiratory problems.

The raised volume rapid thoraco-abdominal compression technique allows infant PFTs to be performed in infants, yielding results that are comparable to conventional PFTs in cooperative subjects [13]. However, the time and sedation risk involved in performing infant PFTs preclude its use in studying large cohorts and in clinical assessment. Tidal breathing analysis allows assessment of respiratory function without sedation [14] and can be performed in the NICU. In full-term infants, abnormal tidal breathing measurements in early infancy are an

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

independent risk factor for wheezing and asthma in later life [5, 6], but limited data are available regarding the association of these physiologic measurements with clinical outcomes in preterm infants.

We hypothesized that tidal breathing measurements in extremely preterm infants near the time of hospital discharge would differentiate between infants with BPD from those without BPD and be predictive of which infants would develop respiratory morbidity in the first year of life. To test this hypothesis, we measured tidal breathing variables in a large cohort of extremely preterm infants and assessed their BPD status before discharge and respiratory morbidity in the first year of life.

Methods

Study Subjects

Infants in this study were enrolled in the Prematurity and Respiratory Outcomes Program (PROP, clinicaltrials.gov NCT01607216), a multicenter, longitudinal, birth cohort study of extremely low gestational age neonates. Details of the design of the PROP study have been reported [15]. The PROP study network consisted of 5 clinical research sites located across the United States and 1 data coordinating center. Each center enrolled between 105-184 infants. born at <29 weeks gestational age (GA). Parental consent was obtained prior to enrollment. Detailed, daily clinical data were prospectively collected while in the hospital, and tidal breathing measurements were obtained 1 week prior to anticipated discharge from the NICU. BPD was defined using a modification of the criteria proposed by Shennan, et al. [16-18].

Infants were classified as having BPD if they needed supplemental O_2 at 36 weeks PMA; they were classified as "no BPD" if they were in room air at 36 weeks PMA or discharged home in room air before 36 weeks PMA.

Following discharge, families were contacted by phone at 3, 6, 9, and 12 months for a questionnaire assessing respiratory morbidity [18]. There are no validated, consensus definitions of respiratory morbidity in preterm infants. Previous studies of respiratory outcomes of prematurity have used a variety of measures, each of which may have its own associated biases [3, 18, 19]. For example, a history of wheezing may be affected by recall bias, while medication use and hospitalization may be affected be socioeconomic factors and access to health care. With this background in mind, the PROP developed a composite measure of post-discharge respiratory morbidity as its primary outcome [18, 19]. Infants were classified as having post-discharge respiratory disease in the first year of life, if their caregivers reported a positive response in 1 of four domains on 2 or more survey encounters. The four domains consisted of respiratory medications, hospitalization for respiratory causes, respiratory symptoms, and respiratory technology use. We also defined secondary outcomes by the severity of respiratory disease based on hospitalization, supplemental oxygen therapy, or mechanical ventilation [18].

The PROP protocol was approved by local institutional review boards at each of the clinical research sites and the PROP Observational Study Monitoring Board. Parents of the PROP enrollees and the full-term comparison infants provided written informed consent for all study procedures, including tidal breathing analyses.

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Tidal Breathing Measurements

The BioCapture physiologic monitoring system (Great Lakes Neurotech, Cleveland, Ohio) was used to make tidal breathing measurements by respiratory inductance plethysmography (RIP). Infants were excluded from RIP if they were receiving ≥1 liter per minute of nasal cannula flow (FiO_2=0.21 to 1.0) or had a condition that prevented placement of inductance bands around the chest or abdomen. They were excluded from RIP if they were being supported with continuous positive airway pressure or mechanical ventilation. The scalar RIP tracings captured rib cage and abdominal motion. Continuous pulse oximetry was also simultaneously recorded with an oximeter connected to the BioCapture system. The oximeter had an effective averaging time of 1.5 to 3.0 sec depending on the pulse rate (NONIN Medical, Inc., Minneapolis, MN). Infants were studied in the supine position and ≥ 30 minutes after their last feeding. Nasogastric (NG) tubes were removed, if possible. Quiet sleep was behaviorally defined by eyes closed, regular breathing, and no fluttering of eyelids or limbs [20]. Sleep state was assessed and documented every 3 minutes, and only data from behaviorally determined quiet sleep were analyzed. Fifteen to 30 minutes of RIP data were collected, after which infants received 1.25 mg of albuterol by small volume wet nebulizer. An additional 15 minutes of data were collected 10 minutes after the nebulization treatment was completed. Albuterol was not administered if the parent refused or if there was a medical contraindication to beta agonists, e.g., supraventricular tachycardia.

Although the primary objective of our study was to assess the relationship between tidal breathing measurements and pulmonary outcomes in preterm infants, we obtained data from a small cohort of 18 healthy term infants at 1-3 days of life as a comparison group. The infants

were recruited from 3 PROP sites (Rochester/Buffalo, Indiana University, and Vanderbilt University). Their mean PMA at testing was 39.5 weeks (SD=1.3 w, range 36-41 weeks) and the mean birth weight was 3,289 g (SD=362 g). We did not administer albuterol to the term comparison cohort.

RIP Data Analysis

RIP data were analyzed as previously reported [21, 22]. Individuals assessing RIP data were blinded to BPD and post-discharge respiratory disease status. Five representative epochs of quiet sleep were selected for analysis, and descriptive statistics for RIP values were calculated. To account for variability in breathing patterns, a minimum of 30 breaths was used for analysis [23, 24]. Selected breaths demonstrated a stable end-expiratory volume and regular rhythmic motion consistent with quiet sleep on the scalar tracings, and a closed tracing when viewed on a Konno-Mead plot with no “figure of eight” loops [14]. Rib cage and thoracic excursion were internally calibrated to each other using the quantitative diagnostic calibration technique [25]. Because we did not make absolute measurements, such as tidal volume, external calibration to a known volume was not necessary and was not performed [14]. To assess agreement when selecting research quality breaths, we compared analyses from 2 independent observers using data from 32 infants and found the intraclass correlation coefficient to be 0.95.

Vivosense software (Vivonoetics, Ventura, CA) was used to analyze the RIP data. The RIP-derived measurements included respiratory rate, phase angle, the ratio of time to peak expiratory flow over total expiratory time (Tpef/Te), and percent contribution of the rib cage to inspiratory tidal volume (%RCi) [14]. Phase angle reflects the relative synchrony between the rib

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

cage and abdominal compartments during tidal breathing, and it is elevated with increased airway resistance or decreased lung compliance [26]. Tpef/Te is smaller in individuals with obstructive lung disease and is a predictor of infantile wheezing and future asthma diagnosis [5, 6, 27, 28]. A lower %RCi is, most often, a reflection of increased chest wall compliance [14, 29].

Oxygenation and Desaturations with Brief Respiratory Pauses during Sleep

A higher number of mild desaturations with brief respiratory pauses during sleep are associated with a lower FRC [30]. We analyzed breathing patterns and simultaneous pulse oximetry during epochs of behaviorally-determined quiet sleep, as above. The number of desaturation episodes with an absolute fall in SpO_2% by 4 during an apnea that lasted at least 4 seconds was counted and normalized for the number of minutes of quiet sleep for each infant. Apneas were identified from the scalar RIP tracings. If an infant had no 4 sec apneas linked to desaturation by 4%, the longest apnea without a desaturation by 4% was identified (an apnea with stable SpO2%). This assessment allowed us to characterize all infants, including those who had the ability to avoid developing hypoxemia with short apnea. Infants having a 4% desaturation within 10 seconds of a 4 second apnea were further described by how fast their SpO2% fell during the apnea, using the %fall per second of apnea. This value, in particular, is inversely correlated with FRC [30]. The lowest SpO2% (SpO2% nadir) was also recorded.

Training and Quality Control

Before initiation of the study, research personnel who performed tidal breathing studies at all the study sites attended a training meeting where they reviewed how to perform the tests

uniformly. Before any subjects were enrolled, each site was required to demonstrate the ability to perform at least 5 tidal breathing studies on infants that met the research-quality criteria described above. Once enrollment was initiated, site visits were performed to ensure proper test procedures. A shared manual for standard operating procedures for tidal breathing measurements was used at all sites. All studies were reviewed at the central over-reading center located at Riley Children's Hospital (Indiana University School of Medicine), and only studies that met research-quality criteria were used for analysis. Ongoing quality control feedback was provided to the sites, indicating why studies were unacceptable, and every study site was continuously monitored for rate of unacceptable studies and changes in study personnel. Additional on-site training and/or conference calls with study investigators (CLR and JSK) were conducted as needed to maintain quality.

Statistical Analysis

Infant demographics at birth and at the time of testing, clinical status at the time of testing, and each domain of post-discharge respiratory disease (hospitalization, symptoms, medication use, and technology use) were summarized as proportions, mean and standard deviations (SD), median and interquartile range (IQR). For each subject with more than 30 breaths, the median value of each measurement was calculated as a summary value to be included in the statistical analysis. The data were compared between infant with and without post-discharge respiratory disease using Pearson Chi-square test, Cochran-Armitage trend test, two-group T-test, or Wilcoxon rank-sum test as appropriate. We calculated 95% confidence intervals for median differences using the bootstrap method [31]. Two-group T-test or Wilcoxon rank-sum test were

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

also used to compare baseline pre-bronchodilator tidal breathing measurements between BPD and non-BPD groups. To assess whether tidal breathing measurements were predictive of post-discharge respiratory disease in preterm infants with more severe lung disease, we analyzed the data from infants with BPD as a subgroup.

For each infant with both pre- and post-bronchodilator RIP data available, we assessed the infant's bronchodilator response (BDR) by comparing the mean of all values of a particular RIP measure from the pre-BD breaths to the mean from the post-BD breaths. BDR was defined as a mean decrease in phase angle or increase in Tpef/Te from baseline larger than the pooled standard deviation [32]. To study the relationship between BDR and post-discharge respiratory disease, the proportion of infants with BDR who had post-discharge respiratory disease was compared to those without using a chi square test.

All statistical tests were two-sided and $P \leq 0.05$ was considered significant. Statistical analyses were performed with SAS 9.3 software (SAS Institute, Cary, North Carolina).

Results

Of the 765 infants from the PROP cohort who survived to 36 weeks PMA, tidal breathing measurements were made in 564 (73.7%) available eligible and consenting infants of the total cohort (Table 1). Compared to the entire PROP cohort, the infants in this study tended to have a higher GA and were more likely to be White/Caucasian [18]. Infants who did not have tidal breathing measurements were born at a slightly lower GA (26.9 weeks vs. 26.2, $P<0.001$), had lower birth weight (947 grams vs 842, $P<0.001$), and were more likely to have BPD (36.8% vs

54.9%, P<0.001) (Table E1 available in the online supplement). Of the infants who had tidal breathing measurements, 348 (61.7%) had post-discharge respiratory disease and 189 (33.5%) did not; there were 27 infants (4.8%) who did not have enough post-discharge data to assess respiratory disease status. A flow diagram of the derivation of our study cohort is available online (Figure E1). The most common reasons for no measurements were ineligibility for study based on level of respiratory support, parent refusal, and transfer to an outside hospital before 34 weeks PMA. Most (63.8%) infants were on no respiratory support, and the mean PMA at time of testing was 37.4 + 1.9 weeks. Compared to term infants, PROP infants demonstrated greater thoracoabdominal asynchrony (difference between PROP and term cohort phase angle -65.1°, 95%CI -71.4° to -58.8°), decreased %RCi (mean difference 23.1%, 95% CI 15.1%-31.1%), and more frequent oxyhemoglobin desaturations (mean difference 0.37, 95%CI 0.21-0.44)(Table E2).

The distribution of different RIP measurements for the PROP cohort is shown in Figure 1. RR and %RCi were normally distributed but PA had a bimodal distribution for the preterm infants. Tpef/Te was tightly clustered around 0.49. The distribution of sleep oximetry with RIP measurements is shown in Figure 2. In general, infants had fewer than 1 spontaneous desaturation by ≥4% per minute of quiet sleep, those tolerating longer than 4 sec apneas without 4% desaturation could do so for as long as 8 secs, and most infants with a fall in SpO_2% by 4% had falls by 2% per sec of apnea, or less, although some had quite precipitous falls in SpO_2%. The nadir of SpO_2% tended to be >80%.

Tidal breathing measurements in infants with BPD are compared to those without BPD in Table 2. There was a small, but statistically significant difference in Tpef/Te between infants

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

with BPD compared to those without BPD, with Tpef/Te being smaller in the BPD group (mean difference of 0.01, 95%CI 0.00-0.01). There were no other significant differences in BPD vs. non-BPD infants in any RIP tidal breathing measurements or results based on oximetry. However, there was a trend towards a slightly larger number of desaturations in the BPD group. We did not observe any consistent, clinically significant associations between any other clinical variables related to NICU stay (e.g. days on mechanical ventilation) and any tidal breathing measurements, except that lower birthweight was associated with a higher respiratory rate.

There were no significant differences in pre-bronchodilator tidal breathing measurements between infants who developed post-discharge respiratory disease and those who did not (Table 3). Although there was a trend towards a higher phase angle in infants with BPD who had post-discharge respiratory disease compared to those who did not, this difference was not significant, and all other tidal breathing measurements were similar in both groups (Table E3). We also did not observe any association between tidal breathing measurements and secondary outcomes, such as hospitalization (Table E4). BDR as assessed by a decrease in phase angle after bronchodilator was present in 46% of the study cohort, while BDR as assessed by an increase in Tpef/Te was present in 24% (Table 3). A decrease in phase angle after bronchodilator was more common in Infants with post-discharge respiratory disease compared to those who did not (50% vs 38.5%, P=0.051), although this difference did not meet our prespecified significance level of P≤0.05. There was no significant association between results based on oximetry while sleeping and post-discharge respiratory disease status at 1 year.

Discussion

In this prospective study of a cohort of extremely low gestational age neonates who were breathing ambient air or supported by low-flow nasal cannulas, we found different tidal breathing patterns at 37 weeks PMA compared to normal term neonates, but these results were not associated with the diagnosis of BPD or subsequent post-discharge respiratory disease. The frequency of BDR near the time of discharge from the NICU was increased in infants with subsequent post-discharge respiratory disease compared to those without, but not significantly so.

Other investigators have performed tidal breathing measurements in preterm infants around the time of discharge. The Bern Infant Study measured Tpef/Te using a pneumotachometer and assessed lung clearance index and FRC by multiple breath washout at 44 weeks PMA, in a cohort of preterm and full-term infants [33]. Tpef/Te was lower in infants with BPD compared to those without BPD. There was no difference in lung clearance index between the two groups, and FRC was slightly lower in the BPD infants. Warren, et al., performed RIP in preterm infants and found that mean PA was 61º compared to 12º in the full-term comparison group [34]. Their results are not directly comparable to ours because Warren, et al., studied infants in the prone position and included infants with a GA>29 weeks. However, overall the findings in these two studies are in agreement with ours. For example, Warren, et al., did not observe a significant association between higher PA and BPD diagnosis. We enrolled many more infants than either the Bern study or the study by Warren, et al., and all were born before 29 weeks PMA. We also prospectively collected post-discharge clinical data that allowed

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

us to analyze associations between tidal breathing measurements and clinical outcomes. Ours was the first study to assess the prognostic significance of BDR in premature infants; among 353 infants receiving albuterol we found no significant association between tidal breathing-based BDR at the time of discharge and subsequent post-discharge respiratory disease.

The Bern Infant Study found that lower Tpef/Te was associated with increased wheezing in the first year of life, but addition of tidal breathing results to clinical variables did not increase the ability of a predictive model to predict future wheezing in preterm infants [35]. Bentsen, et al also found that a low Tpef/Te in preterm infants was predictive of respiratory morbidity in the first year of life [36]. In addition to Tpef/Te, we also studied phase angle and sleep hypoxemia, but we found that none of these measurements was predictive of future respiratory morbidity in the PROP cohort. It is difficult to compare our study to others because of differences in GA, methods used to measure Tpef/Te (i.e. pneumotachometer vs. RIP) and different definitions of post-discharge respiratory disease. Furthermore, Bentsen, et al studied a much smaller cohort with a much lower prevalence of first year respiratory morbidity. Taken together, our study and others suggest that tidal breathing measurements most likely have limited utility in predicting short-term respiratory outcomes in extremely preterm infants.

Other than physiologically unimportant differences in Tpef/Te there was little association between tidal breathing measurements and BPD status [33]. This may be because our definition of BPD, though conventional [16, 17], is based only on need for supplemental O2. Hjalmorson, et al have shown a lack of association between the need for supplemental O2 and measures of respiratory mechanics, such as compliance and conductance [37]. It is likely that tidal breathing measurements reflect respiratory mechanics, but in a given infant respiratory

mechanics per se may be less responsible for hypoxemia than, for example, dysfunctional responses of the pulmonary circulation leading to ventilation-perfusion mismatching. Furthermore, in some preterm infants immature control of breathing may contribute more than parenchymal lung disease in causing a need for supplemental O2 [38].

Tidal breathing measurements from the PROP preterm infants were abnormal compared to our term cohort, but there was no difference in these measurements among PROP enrollees who developed post-discharge respiratory disease compared to those who did not. These results suggest that factors other than abnormal respiratory mechanics at discharge may make a greater contribution to the risk of persistent pulmonary disease in these extremely preterm infants. A recent study of pulmonary outcomes associated with chorioamnionitis supports this hypothesis; chorioamnionitis was associated with increased pulmonary morbidity in the first 2 years of life, but it was not associated with lower lung function measured by infant PFTs [39].

BDR in full-term infants is associated with an increased likelihood of wheezing in infancy and childhood [40, 41]. BDR as assessed by decline in phase angle after bronchodilator administration was more common in PROP infants with post-discharge respiratory disease than those without, although this difference just failed to meet our pre-specified threshold for statistical significance. An increased phase angle can be caused by several mechanisms, including upper airway obstruction and increased lung compliance [42, 43], and there are limited studies using phase angle as a measure of BDR [26]. With these caveats in mind, our results suggest the possibility that BDR is a risk factor for post-discharge respiratory morbidity in extremely preterm infants and further study of this relationship should be conducted.

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

There are limitations to our inclusion criteria and outcome measurements that may have affected our results. For example, we excluded infants receiving >1 lpm of flow. This may have excluded infants with the potential for more severe post-discharge respiratory disease from our study and likely selected for a group with at most moderate respiratory function impairment. This is consistent with the finding of a lower rate of post-discharge respiratory disease among infants in our cohort who were well enough to have RIP performed compared to the entire PROP cohort [18]. The inclusion criterion of infants receiving ≤1 lpm, in particular, may have contributed substantially to the lack of association between pre-BD tidal breathing results and BPD or post-discharge respiratory disease. However, even in this group of preterm infants with minimal respiratory support at NICU discharge, there was substantial post-discharge respiratory morbidity, which was the motivation for our conducting a study to identify non-invasive physiologic markers of future respiratory illness. Our definition of post-discharge respiratory disease has not been validated or used in studies outside of PROP. However, it is similar to those use by other studies [3] and the diagnosis of BPD increased the likelihood of having post-discharge respiratory disease [18], consistent with many other studies of preterm respiratory outcomes.

Tidal breathing measurements remain an indirect assessment of respiratory function and are affected by factors other than intra-thoracic lung mechanics. For example, thoraco-abdominal synchrony is affected by upper airway obstruction as well as lower airway obstruction [42], and we cannot rule out that the increased phase angle we observed was due to upper airway obstruction. In contrast to some other studies, we did not directly measure Tpef/Te with a pneumotachometer; rather it was derived from changes in the sum of thoracic

and abdominal expansion over time, changes in flow whose detection could be delayed when the measurements rely on rib cage or abdominal excursion. Finally, among infants studied at 32 weeks PMA, it has been shown that some infants are able to keep their SpO_2% > 90% in room air despite having marked asynchrony with PA >>80 degrees in many cases [44].

In summary, we have shown that extremely low gestational age neonates breathing ambient air or on low-flow nasal cannula support have abnormal tidal breathing patterns, but these patterns do not differ between BPD and non-BPD infants. Pre-bronchodilator and post-bronchodilator tidal breathing results were not predictive of post-discharge respiratory disease. Our results suggest that factors other than altered respiratory mechanics alone, such as response to respiratory viral infections among infants whose mechanics are already more or less compromised, may contribute more to future respiratory problems in the preterm population [45].

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

References

1. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007; 357.
2. Bhandari A, Panitch HB. Pulmonary outcomes in bronchopulmonary dysplasia. *Seminars in perinatology* 2006; 30: 219-226.
3. Stevens TP, Finer NN, Carlo WA, Szilagyi PG, Phelps DL, Walsh MC. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). *J Pediatr* 2014; 165.
4. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med* 2012; 185: 1183-1189.
5. Håland G, Carlsen KCL, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006; 355.
6. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319.
7. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332.
8. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Young S, Landau LI, Le Souef PN. Infants with flow limitation at 4 weeks: outcome at 6 and 11 years. *Am J Respir Crit Care Med* 2002; 165: 1294-1298.
9. Baraldi E, Filippone M, Trevisanuto D, Zanardo V, Zacchello F. Pulmonary function until two years of life in infants with bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 1997; 155.
10. Tepper RS, Morgan WJ, Cota K, Taussig LM. Expiratory flow limitation in infants with bronchopulmonary dysplasia. *J Pediatr* 1986; 109: 1040-1046.
11. Kao LC, Warburton D, Cheng MH, Cedeno C, Platzker AC, Keens TG. Effect of oral diuretics on pulmonary mechanics in infants with chronic bronchopulmonary dysplasia: results of a double-blind crossover sequential trial. *Pediatrics* 1984; 74: 37-44.
12. Gerhardt T, Hehre D, Feller R, Reifenberg L, Bancalari E. Serial determination of pulmonary function in infants with chronic lung disease. *J Pediatr* 1987; 110: 448-456.
13. Feher A, Castile R, Kisling J, Angelicchio C, Filbrun D, Flucke R, Tepper R. Flow limitation in normal infants: a new method for forced expiratory maneuvers from raised lung volumes. *J Appl Physiol* 1996; 80: 2019-2025.
14. Palmer J, Allen J, Mayer O. Tidal Breathing Analysis. *NeoReviews* 2004; 5: e186-e193.
15. Pryhuber GS, Maitre NL, Ballard RA, Cifelli D, Davis SD, Ellenberg JH, Greenberg JM, Kemp J, Mariani TJ, Panitch H, Ren C, Shaw P, Taussig LM, Hamvas A. Prematurity and respiratory

outcomes program (PROP): study protocol of a prospective multicenter study of respiratory outcomes of preterm infants in the United States. *BMC Pediatrics* 2015; 15: 1-14.

16. Poindexter BB, Feng R, Schmidt B, Aschner JL, Ballard RA, Hamvas A, Reynolds AM, Shaw PA, Jobe AH. Comparisons and Limitations of Current Definitions of Bronchopulmonary Dysplasia for the Prematurity and Respiratory Outcomes Program. *Annals of the American Thoracic Society* 2015; 12: 1822-1830.
17. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. *Pediatrics* 1988; 82.
18. Keller RL, Feng R, DeMauro SB, Ferkol T, Hardie W, Rogers EE, Stevens TP, Voynow JA, Bellamy SL, Shaw PA, Moore PE, Prematurity, Respiratory Outcomes P. Bronchopulmonary Dysplasia and Perinatal Characteristics Predict 1-Year Respiratory Outcomes in Newborns Born at Extremely Low Gestational Age: A Prospective Cohort Study. *J Pediatr* 2017; 187: 89-97 e83.
19. Maitre NL, Ballard RA, Ellenberg JH, Davis SD, Greenberg JM, Hamvas A, et al. Respiratory consequences of prematurity: evolution of a diagnosis and development of a comprehensive approach. J Perinatol. 2015; doi:10.1038/jp.2015.19 [Epub ahead of print].
20. Prechtl HF. The behavioural states of the newborn infant (a review). *Brain Research* 1974; 76: 185-212.
21. Mayer OH, Clayton RG, Sr., Jawad AF, McDonough JM, Allen JL. Respiratory inductance plethysmography in healthy 3- to 5-year-old children. *Chest* 2003; 124: 1812-1819.
22. Ren CL, Rosenfeld M, Mayer OH, Davis SD, Kloster M, Castile RG, Hiatt PW, Hart M, Johnson R, Jones P, Brumback LC, Kerby GS. Analysis of the associations between lung function and clinical features in preschool children with cystic fibrosis. *Pediatr Pulmonol* 2012; 47: 574-581.
23. Stocks J, Dezateux CA, Jackson EA, Hoo AF, Costeloe KL, Wade AM. Analysis of tidal breathing parameters in infancy: how variable is TPTEF:TE? *Am J Respir Crit Care Med* 1994; 150: 1347-1354.
24. Ulm LN, Hamvas A, Ferkol TW, Rodriguez OM, Cleveland CM, Linneman LA. Sources of methodological variability in phase angles from respiratory inductance plethysmography in preterm infants. *Ann Am Thor Soc* 2014; 11.
25. Adams JA, Zabaleta IA, Stroh D, Johnson P, Sackner MA. Tidal Volume Measurements in Newborns Using Respiratory Inductive Plethysmography. *American Journal of Respiratory and Critical Care Medicine* 1993; 148: 585-588.
26. Allen JL, Wolfson MR, McDowell K, Shaffer TH. Thoracoabdominal asynchrony in infants with airflow obstruction. *Am RevRespir Dis* 1990; 141: 337-342.
27. Morris MJ, Lane DJ. Tidal expiratory flow patterns in airflow obstruction. *Thorax* 1981; 36: 135-142.

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

28. van der Ent CK, Brackel HJ, van der LJ, Bogaard JM. Tidal breathing analysis as a measure of airway obstruction in children three years of age and older. *Am J Respir Crit Care Med* 1996; 153: 1253-1258.

29. Hershenson MB, Stark AR, Mead J. Action of the inspiratory muscles of the rib cage during breathing in newborns. *Am RevRespir Dis* 1989; 139: 1207-1212.

30. Tourneux P, Leke A, Kongolo G, Cardot V, Degrugilliers L, Chardon K. Relationship between functional residual capacity and oxygen desaturation during short central apneic events during sleep in “late preterm” infants. *Pediatric research* 2008; 64.

31. Ghosh M, Parr WC, Singh K, Babu GJ. A Note on Bootstrapping the Sample Median. *Ann Statist* 1984; 12: 1130-1135.

32. Hansen JE, Sun XG, Adame D, Wasserman K. Argument for changing criteria for bronchodilator responsiveness. *Respir Med* 2008; 102: 1777-1783.

33. Latzin P, Roth S, Thamrin C, Hutten GJ, Pramana I, Kuehni CE. Lung volume, breathing pattern and ventilation inhomogeneity in preterm and term infants. *PLoS One* 2009; 4.

34. Warren RH, Horan SM, Robertson PK. Chest wall motion in preterm infants using respiratory inductive plethysmography. *EurRespirJ* 1997; 10: 2295-2300.

35. Proietti E, Riedel T, Fuchs O, Pramana I, Singer F, Schmidt A, Kuehni C, Latzin P, Frey U. Can infant lung function predict respiratory morbidity during the first year of life in preterm infants? *European Respiratory Journal* 2014; 43: 1642-1651.

36. Bentsen MH, Markestad T, Øymar K, Halvorsen T. Lung function at term in extremely preterm-born infants: a regional prospective cohort study. *BMJ Open* 2017; 7.

37. Hjalmarson O, Brynjarsson H, Nilsson S, Sandberg KL. Persisting hypoxaemia is an insufficient measure of adverse lung function in very immature infants. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2014; 99: F257-F262.

38. Coste F, Ferkol T, Hamvas A, Cleveland C, Linneman L, Hoffman J, Kemp J. Ventilatory control and supplemental oxygen in premature infants with apparent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2015; 100: F233-237.

39. McDowell KM, Jobe AH, Fenchel M, Hardie WD, Gisslen T, Young LR, Chougnet CA, Davis SD, Kallapur SG. Pulmonary Morbidity in Infancy after Exposure to Chorioamnionitis in Late Preterm Infants. *Ann Am Thorac Soc* 2016; 13: 867-876.

40. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Cox M, Young S, Goldblatt J, Landau LI, Le Souef PN. The relationship between infant airway function, childhood airway responsiveness, and asthma. *Am J Respir Crit Care Med* 2004; 169: 921-927.

41. Yao W, Barbe-Tuana FM, Llapur CJ, Jones MH, Tiller C, Kimmel R, Kisling J, Nguyen ET, Nguyen J, Yu Z, Kaplan MH, Tepper RS. Evaluation of airway reactivity and immune characteristics as risk factors for wheezing early in life. *J Allergy Clin Immunol* 2010; 126: 483-488 e481.

42. Sivan Y, Deakers TW, Newth CJ. Thoracoabdominal asynchrony in acute upper airway

obstruction in small children. *Am RevRespir Dis* 1990; 142: 540-544.

43. Allen JL, Greenspan JS, Deoras KS, Keklikian E, Wolfson MR, Shaffer TH. Interaction between chest wall motion and lung mechanics in normal infants and infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 1991; 11: 37-43.
44. Brennan C, Ulm L, Julian S, Hamvas A, Ferkol T, Hoffman J, Linneman L, Kemp J. Thoracoabdominal Asynchrony Is Not Associated with Oxyhemoglobin Saturation in Recovering Premature Infants. *Neonatology* 2017; 111: 297-302.
45. Pryhuber GS. Postnatal Infections and Immunology Affecting Chronic Lung Disease of Prematurity. *Clin Perinatol* 2015; 42: 697-718.

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Figure Legends

Figure 1. Frequency histograms for respiratory inductance plethysmography measurements

Figure 2. Frequency histograms for sleep oximetry measurements

Table 1. Demographic and Clinical Characteristics of the Study Cohort.

	No Post-Discharge Respiratory Disease (n=189)	**Post-Discharge Respiratory Disease (n=348)**
	n (%) or mean ± SD	n (%) or mean ± SD
Male	80 (42.3%)	188 (54.0%)
Race		
White / Caucasian	131 (69.3%)	194 (55.7%)
Black / African American	47 (24.9%)	138 (39.7%)
Asian	8 (4.2%)	4 (1.1%)
Others	3 (1.6%)	12 (3.4%)
Gestational age, weeks	27.0 (1.3)	26.8 (1.4)
Multiple births	63 (33.3%)	76 (21.8%)
Twins	52	66
Triplets or quadruplets	11	10
Birth weight, gram	972.5 (232.9)	933.3 (225.2)
PMA at test, week	37.1 (1.8)	37.5 (2.0)
Weight at test, gram	2491.0 (462.6)	2504.5 (486.5)
Level of support at test		
No respiratory support	152 (80.4%)	190 (54.6%)
Nasal cannula ≤ 1LPM	37 (19.6%)	158 (45.4%)
Nasogastric tube in place during test	42 (22.2%)	63 (18.1%)
On caffeine during test	6 / 180 (3.3%)	12 / 326 (3.7%)
BPD (Modified Shennan's)	50 / 188 (26.6%)	145 / 342 (42.4%)
PMA at discharge, week	38.8 (2.9)	39.7 (3.8)
Hospitalizations in year 1		
0	173 / 185 (93.5%)	220 / 335 (65.7%)
1	11 / 185 (5.9%)	74 / 335 (22.1%)
≥ 2	1 / 185 (0.5%)	41 / 335 (12.2%)

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Symptom in year 1		
Frequent wheeze or cough, with inhaled steroids, for ≥ 6 months	0	33 / 343 (9.6%)
Frequent wheeze or cough for ≥ 6 months	0	244 / 343 (71.1%)
None	187 / 187 (100.0%)	66 / 343 (19.2%)
Medication use in year 1		
System steroids or pulmonary vasodilator	8 / 189 (4.2%)	76 / 345 (22.0%)
Inhaled steroids bronchodilator	6 / 189 (3.2%)	118 / 345 (34.2%)
None	175 / 189 (92.6%)	151 / 345 (43.8%)
Technology use in year 1		
Home oxygen after month 6 or mechanical ventilation	1 / 189 (0.5%)	61 / 344 (17.7%)
Home oxygen use at month 3 or tracheostomy	13 / 189 (6.9%)	53 / 344 (15.4%)
None	175 / 189 (92.6%)	230 / 344 (66.9%)

Table 2. Tidal breathing measurements in infants with and without bronchopulmonary dysplasia*.

Tidal breathing measurements	n	No Bronchopulmonary Dysplasia*	Bronchopulmonary Dysplasia*	Mean or Median Difference (95%CI**)	p-value***
RIP					
Phase angle (degrees)	429	77.4 ± 45.1	81.5 ± 45.9	4.0 (-4.8, 12.9)	0.37
Respiratory rate (breaths per minute)	429	60.1 ± 7.9	61.0 ± 10.4	1.0 (-0.8, 2.7)	0.28
Tpef/Te	429	0.50 ± 0.02	0.49 ± 0.04	-0.009 (-0.015, -0.003)	<0.01
%RCi	429	0.16 ± 0.27	0.16 ± 0.31	-0.01 (-0.06, 0.05)	0.77
Sleep Oximetry (Room air only)					
Number of desaturations ≥4% per second	260	0.42 (0.18-0.82)	0.61 (0.35-0.88)	0.19 (0.05, 0.36)	0.03
Longest apnea (seconds)	66	4.5 (3.5-5.5)	3.2 (2.5-3.3)	-1.4 (-1.6, -0.9)	0.03
Percent fall in O_2 saturation/second, %	188	1.6 (1.2-2.1)	1.5 (1.0-2.1)	-0.1 (-0.3, 0.2)	0.69
Lowest SpO_2, %	255	87.5 (83.0-91.0)	85.0 (82.5-88.0)	-2.5 (-4.0, 1.0)	0.17

Abbreviations: RIP, respiratory inductance plethysmography; Tpef/Te, ratio of time to peak expiratory flow over total expiratory time; %RCi, percent contribution of rib cage expansion to inspiratory tidal volume.

* presented as mean ± SD or median (IQR)

** 95% C.I.s of Median differences obtained through bootstrap method [31].

*** T-test with equal variance or Wilcoxon Test

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Table 3. Tidal breathing data obtained near the time of discharge in infants with and without post-discharge respiratory disease after discharge*.

Tidal breathing measurements	n	No Post-Discharge Respiratory Disease*	Post-Discharge Respiratory Disease*	Mean/Median Difference or OR (95%CI**)	p-value***
RIP					
Phase angle (degree)	433	77.5 (44.5)	80.0 (45.9)	2.5 (-6.6, 11.5)	0.59
Respiratory rate (breaths per minute)	433	60.2 (8.2)	60.6 (9.3)	0.4 (-1.4, 2.2)	0.69
Tpef/Te	433	0.49 (0.03)	0.49 (0.03)	0.00 (-0.01, 0.01)	0.84
%RCi	433	0.17 (0.28)	0.16 (0.29)	-0.01 (-0.07, 0.04)	0.67
Sleep Oximetry (in room air only)					
Number of desaturations ≥4% per second	262	0.39 (0.23-0.81)	0.45 (0.20-0.85)	0.06 (-0.03, 0.18)	0.75
Longest apnea (seconds)	66	4.2 (3.5-5.48)	4.3 (3.2-5.38)	0.2 (-0.7, 0.6)	0.60
Percent fall in O_2 saturation/second, %	190	1.7 (1.1-2.05)	1.6 (1.2-2.1)	-0.1 (-0.2, 0.2)	0.95
Lowest SpO_2, %	257	87.0 (81.0-91.0)	88.0 (84.0-91.0)	1.0 (-1.0, 3.0)	0.56
Bronchodilator response					
Phase Angle decrease				1.60 (1.00, 2.55)	0.05
No		67 (61.5%)	106 (50.0%)		
Yes		42 (38.5%)	106 (50.0%)		
Tpef/Te increase				1.54 (0.88, 2.71)	0.13
No		88 (80.7%)	155 (73.1%)		
Yes		21 (19.3%)	57 (26.9%)		

Abbreviations: RIP, respiratory inductance plethysmography; Tpef/Te, ratio of time to peak expiratory flow over total expiratory time; %RCi, percent contribution of rib cage expansion to inspiratory tidal volume.

* presented as mean ± SD or median (IQR) or n (%)

** 95% C.I.s of Median differences obtained through bootstrap method [31].

*** T-test with equal variance or Wilcoxon Test

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

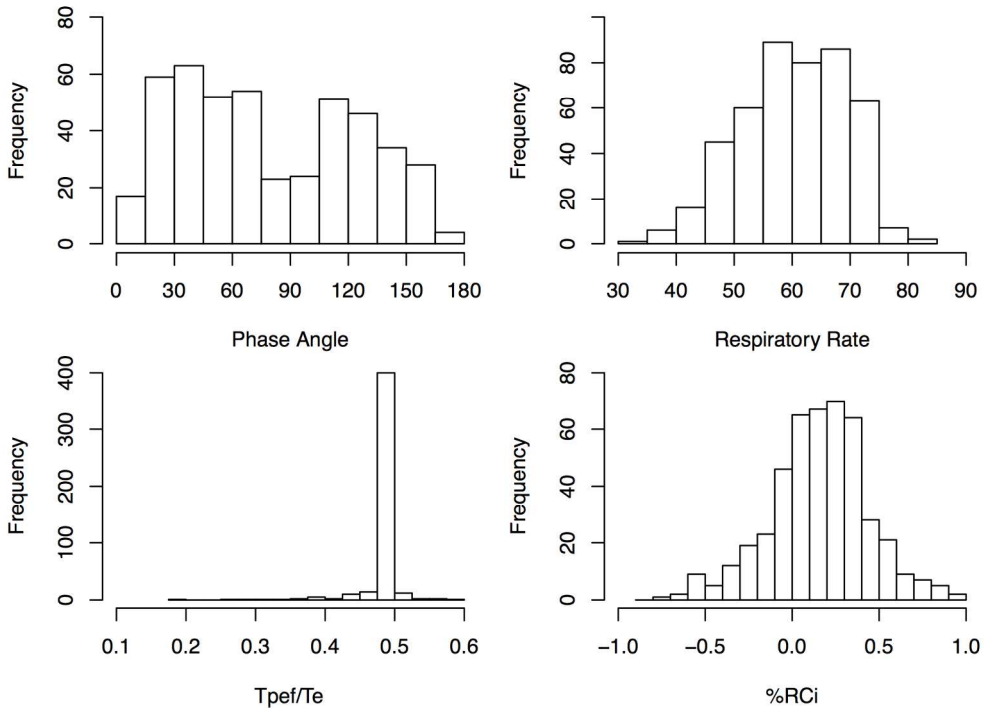


Figure 1. Frequency histograms for respiratory inductance plethysmography measurements

170x121mm (300 x 300 DPI)

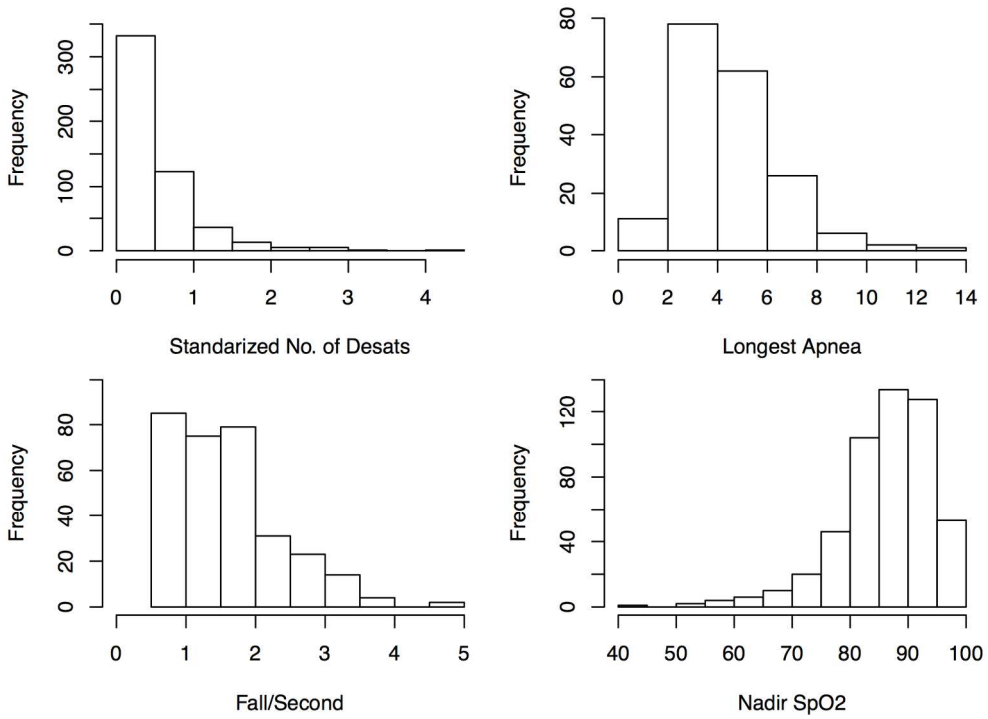


Figure 2. Frequency histograms for sleep oximetry measurements

170x121mm (300 x 300 DPI)

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Online Data Supplement

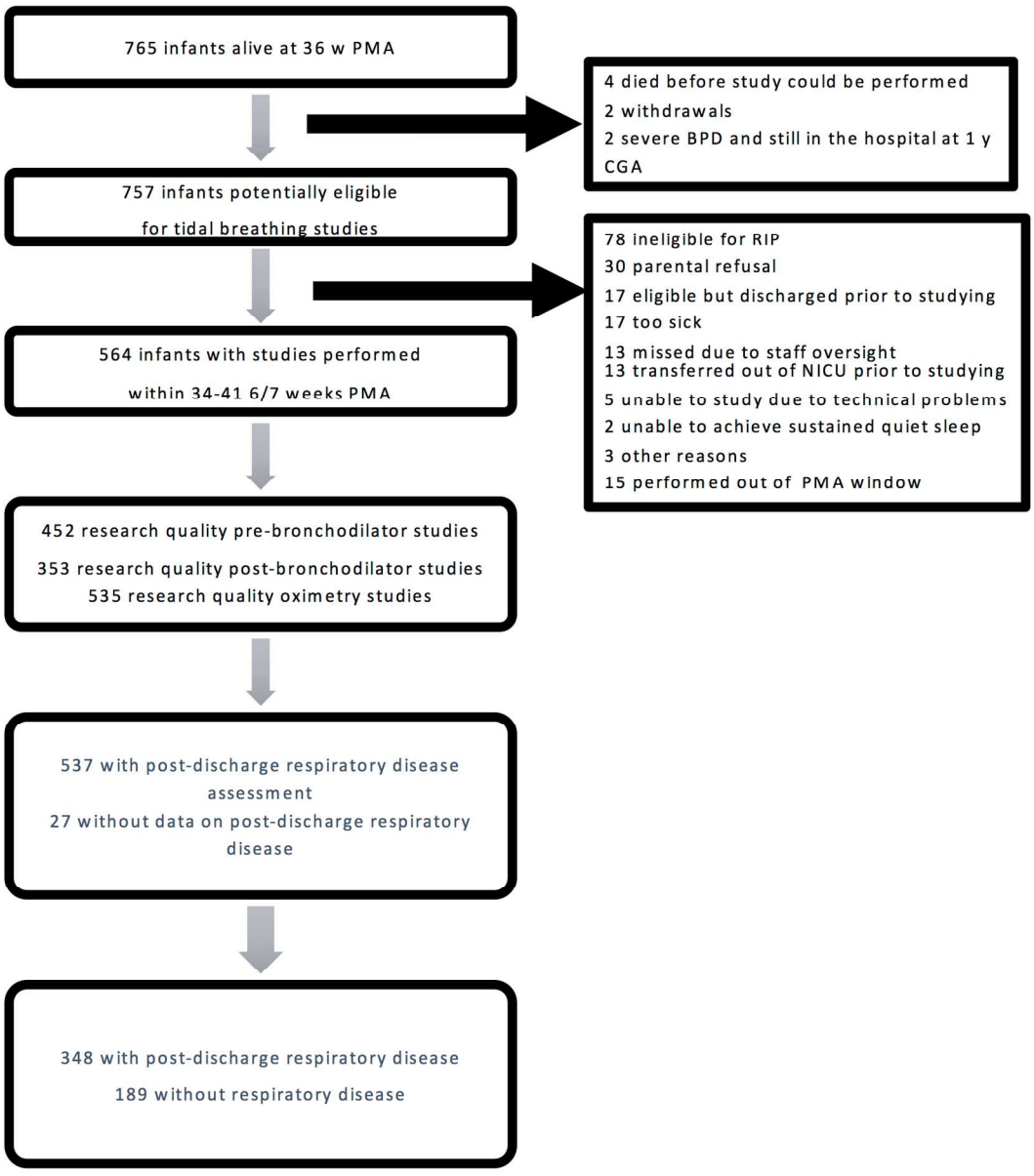
Tidal Breathing Measurements at Discharge and Clinical Outcomes in Extremely Low Gestational Age Neonates

Clement L. Ren, MD, MBA, Rui Feng, PhD, Stephanie D. Davis, MD, Eric Eichenwald, MD, Alan Jobe, MD, PhD, Paul E. Moore, MD, Howard B. Panitch, MD, Jack K. Sharp, MD, Jeff Kisling, RRT, Charles Clem, RRT, and James S. Kemp, MD for the Prematurity and Respiratory Outcomes Program

Supplemental Figures and Tables

Figure E1. Derivation of the study cohort

Figure E1. Derivation of the Study Cohort



ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Table E1. Demographic and clinical characteristics of PROP Subjects with and without tidal breathing measurements or assessment of post-discharge respiratory disease.

	PROP Babies with tidal breathing measurements and post-discharge respiratory disease assessment (n=537) n (%) or mean ± SD	**PROP Babies without tidal breathing measurements and post-discharge respiratory disease assessment (n=228)** n (%) or mean ± SD	**p-value***
Male	268 (49.9%)	125 (54.8%)	0.244
Race			0.120
White / Caucasian	325 (60.5%)	122 (53.5%)	
Black / African American	185 (34.5%)	96 (42.1%)	
Asian	12 (2.2%)	7 (3.1%)	
Others	15 (2.8%)	3 (1.3%)	
Gestational age, weeks	26.9 (1.4)	26.2 (1.4)	<0.001
Multiple births	139 (25.9%)	55 (24.1%)	0.673
Birth weight, grams	947.1 (228.5)	842.0 (224.7)	<0.001
BPD (Modified Shennan)	195 / 530 (36.8%)	117 / 213 (54.9%)	<0.001

***** *Pearson Chi-Square or T-test*

Table E2. Baseline tidal breathing measurements in the study cohort compared to a non-PROP cohort of full term health infants. Abbreviations: RIP, respiratory inductance plethysmography; Tpef/Te, ratio of time to peak expiratory flow over total expiratory time; %RCi, percent contribution of rib cage expansion to inspiratory tidal volume.

		PROP Infants mean ± SD or median (IQR)	**Full term cohort (N=18) mean ± SD or median (IQR)**	**Mean or median difference (95% CI)**	**P-value***
RIP (N=288)	Phase angle, degree	79.1 ± 45.6	14.0 ± 6.8	-65.1 (-71.4, -58.8)	<0.001
	Respiratory rate, breaths per minute	59.7 ± 8.3	46.6 ± 9.3	-13.1 (-17.8, -8.4)	<0.001
	Tpef/Te	0.49 ± 0.03	0.51 ± 0.04	0.02 (-0.00, 0.04)	0.069
	%RCi	15.8 ± 27.6	38.9 ± 14.8	23.1 (15.1, 31.1)	<0.001
Sleep Oximetry	Number of desaturations >4% per minute of quiet sleep (n=279)	0.44 (0.21-0.83)	0.07 (0-0.23)	-0.37 (-0.44, -0.21)	<0.001
	Longest apnea without desaturation, seconds (n=79)	4.2 (3.3-5.5)	5.7 (3.4-6.7)	1.5 (-0.7- 2.6)	0.258
	Percent fall in O_2 saturation/second, % (n=194)	1.6 (1.1-2.1)	0.9 (0.73-1.1)	-0.7 (-0.5-0.9)	0.023
	Lowest O2 saturation, % (n=274)	87 (83-91)	93 (91-95)	6 (3-8)	<0.001

*T-test with unequal variance or Wilcoxon test

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Table E3. Tidal breathing measurements in BPD infants with and without post-discharge respiratory disease. Abbreviations: RIP, respiratory inductance plethysmography; Tpef/Te, ratio of time to peak expiratory flow over total expiratory time; %RCi, percent contribution of rib cage expansion to inspiratory tidal volume.

Tidal breathing measurements		**NO post-discharge respiratory disease mean ± SD or median (IQR)**	**post-discharge respiratory disease mean ± SD or median (IQR)**	**Mean/Median Difference or OR (95%CI*)**	**p-value****
RIP (n=166)	Phase angle, degree	75.2 (43.3)	83.4 (46.7)	8.2 (-8.2, 24.7)	0.325
	Respiratory rate, breaths per minute	61.2 (8.2)	61.0 (9.3)	-0.2 (-4.0, -3.5)	0.904
	Tpef/Te	0.49 (0.03)	0.49 (0.04)	-0.00 (-0.02, 0.01)	0.939
	%RCi	0.16 (0.26)	0.15 (0.33)	-0.01 (-0.12, 0.10)	0.870
Sleep Oximetry (RA only)	Number of desaturations≥4% per second (n=35)	0.52 (0.34-0.39)	0.67 (0.39-0.80)	0.15 (-0.08, 0.13)	0.946
	Longest apnea, second (n=6)	3.3 (3.3-3.3)	3.1 (2.3-3.2)	-0.2 (-1.0, 0.4)	0.667
	Percent fall in O2 saturation/second, % (n=29)	1.60 (1.0-2.0)	1.40 (1.08-2.13)	-0.20 (-0.1, 0.3)	0.954
	Lowest SpO2, % (n=35)	85.0 (83.3-88.0)	87.0 (82.0- 88.0)	2 (-2, 2)	1.000

*95% C.I.s of Median differences were obtained through bootstrap.

**T-test with equal variance or Wilcoxon Test

Table E4. Association between RMS components (Hospitalization, Symptom, Medication, and Oxygen Use) and Tidal breathing data obtained near the time of discharge in infants. Shown as mean differences in each RIP/OWS measure (p-value) between two severity levels of each component. Abbreviations: RIP, respiratory inductance plethysmography; Tpef/Te, ratio of time to peak expiratory flow over total expiratory time; %RCi, percent contribution of rib cage expansion to inspiratory tidal volume.

Tidal breathing measurements		Hospitalization	Symptom	Medication	Technology
RIP	Phase Angle, degree	1.115 (0.257)	0.0005 (0.467)	-0.006 (0.353)	0.080 (0.680)
	Tpef/Te	0.372 (0.736)	0.0003 (0.637)	0.002 (0.745)	0.014 (0.948)
	%RCi	1.309 (0.359)	-0.0001 (0.894)	-0.003 (0.730)	-0.133 (0.638)
	Respiratory rate, breaths per minute	1.098 (0.445)	-0.0005 (0.624)	-0.003 (0.663)	-0.165 (0.563)
Sleep Oximetry	Number of desaturations >=4% per second	1.777 (0.646)	0.005 (0.053)	-0.028 (0.242)	0.801 (0.300)
	Longest apnea, second	-2.730 (0.131)	-0.002 (0.241)	0.026 (0.023)	-0.730 (0.050)
	Percent fall in O_2 saturation/second, %	3.359 (0.381)	0.003 (0.155)	-0.028 (0.250)	1.430 (0.053)
	Lowest SpO_2, %	-0.367 (0.162)	-0.0005 (0.004)	0.002 (0.136)	-0.085 (0.105)

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

Appendix: PROP Investigators and Research Staff

Cincinnati Children's Hospital Medical Center

Investigators

- Claire Chougnet, PhD
- James M. Greenberg, MD
- William Hardie, MD
- Alan H. Jobe MD, PhD
- Karen McDowell, MD

Research Staff

- Barbara Alexander, RN
- Tari Gratton, PA
- Cathy Grisby, BSN, CCRC
- Beth Koch, BHS, RRT, RPFT
- Kelly Thornton BS

Duke University

Investigators

- C. Michael Cotten, MD
- Jack Sharp, MD
- Judith A. Voynow, MD[1]

Research Staff

- Kim Ciccio, RN
- Kim Fisher, PhD

[1]*Currently at Virginia Commonwealth University*

Indiana University

Investigators

- Stephanie Davis, MD
- Brenda B. Poindexter, MD, MS[2]

Research Staff

- Charles Clem, RRT
- Susan Gunn, NNP, CCRC
- Lauren Jewett, RN, CCRC

[2]*Currently at Cincinnati Children's Hospital Medical Center*

University of California San Francisco

Investigators

- Philip L. Ballard MD, PhD
- Roberta A. Ballard MD
- David J. Durand MD[3]
- Eric C. Eichenwald MD[4]
- Roberta L. Keller MD
- Amir M. Khan MD[4]
- Leslie Lusk MD
- Jeffrey D. Merrill MD[5]

- Dennis W. Nielson MD, PhD
- Elizabeth E. Rogers MD

Research Staff

- Jeanette M. Asselin MS RRT-NPS[2]
- Samantha Balan
- Katrina Burson RN, BSN[4]
- Cheryl Chapin
- Erna Josiah-Davis RN, NP[5]
- Carmen Garcia RN, CCRP[4]
- Hart Horneman
- Rick Hinojosa BSRT, RRT, CPFT-NPS[4]
- Christopher Johnson MBA, RRT[4]
- Susan Kelley RRT
- Karin L. Knowles
- M. Layne Lillie, RN, BSN [4]
- Karen Martin RN [4]
- Sarah Martin RN, BSN;
- Julie Arldt-McAlister RN, BSN[4]
- Georgia E. McDavid RN[4]
- Lori Pacello RCP[2]
- Shawna Rodgers RN, BSN[4]
- Daniel K. Sperry RN[4]

[3]Children's Hospital and Research Center Oakland, Oakland, CA
[4]University of Texas Health Science Center - Houston, Houston, TX
[5]Alta Bates Summit Medical Center, Berkeley, CA

University of Rochester Medical Center/University of Buffalo

Investigators:

- Carl D'Angio, MD
- Vasanth Kumar, MD
- Tom Mariani, PhD
- Gloria Pryhuber, MD
- Clement L. Ren, MD[6]
- Anne Marie Reynolds, MD, MPH
- Rita M. Ryan, MD[7]
- Kristin Scheible, MD
- Timothy Stevens, MD, MPH

Research Staff:

- Heidie Huyck, BS
- Valerie Lunger, MS
- Shannon Castiglione, RN
- Aimee Horan, LPN
- Deanna Maffet, RN
- Jane O'Donnell, PNP
- Michael Sacilowski, MAT

ANNALSATS Articles in Press. Published on 08-August-2018 as 10.1513/AnnalsATS.201802-112OC

- Tanya Scalise, RN, BSN
- Elizabeth Werner, MPH
- Jason Zayac, BS
- Kim Bordeaux, RRT
- Pam Brown, RRT
- Julia Epping, AAS, RT
- Lisa Flattery-Walsh, RRT
- Donna Germuga, RRT, CPFT
- Nancy Jenks, RN
- Mary Platt, RN
- Eileen Popplewell, RRT
- Sandra Prentice, CRT

[6]Currently at Indiana University, Indianapolis, IN
[7]Currently at Medical University of South Carolina, Charleston, SC

Vanderbilt University Medical Center

Investigators

- Judy Aschner, MD[8]
- Candice Fike, MD
- Scott Guthrie, MD[9]
- Tina Hartert, MD
- Nathalie Maitre, MD
- Paul Moore, MD
- Marshall Summar, MD[10]

Research Staff

- Amy B Beller BSN
- Mark O' Hunt
- Theresa J. Rogers, RN
- Odessa L. Settles, RN, MSN, CM
- Steven Steele, RN
- Sharon Wadley, BSN, RN, CLS[9]

[8]Currently at Albert Einstein College of Medicine and the Children's Hospital at Montefiore, Bronx, NY
[9]Jackson-Madison County General Hospital, Jackson, TN
[10]Children's National Health System, Washington, DC

Washington University School of Medicine

Investigators

- Thomas Ferkol, MD
- Aaron Hamvas, MD[11]
- Mark R. Holland, PhD
- James Kemp, MD
- Philip T. Levy, MD
- Phillip Tarr, MD
- Gautam K. Singh, MD
- Barbara Warner, MD

Research Staff

- Pamela Bates, CRT, RPFT, RPSGT
- Claudia Cleveland, RRT
- Julie Hoffmann, RN
- Laura Linneman, RN
- Jayne Sicard-Su, RN
- Gina Simpson, RRT, CPFT

[11]Currently at Northwestern University Feinberg School of Medicine

University of Pennsylvania, Perelman School of Medicine
Data Coordinating Center

Investigators

- Jonas Ellenberg, PhD
- Rui Feng, PhD
- Melissa Fernando, MPH
- Howard Panitch, MD
- Barbara Schmidt, MD, MSc
- Pamela Shaw, PhD
- Scarlett Bellamy, ScD

Research Staff

- Maria Blanco, BS
- Denise Cifelli, MS
- Sara DeMauro, MD
- Ann Tierney, BA, MS

Steering Committee Chair

- Lynn M. Taussig, MD, University of Denver

NHLBI Program Officer

- Carol J. Blaisdell, MD